Sofosbuvir (Sovaldi™) and Ledipasvir/Sofosbuvir (Harvoni™)

Criteria for Use

February 2016

VA Pharmacy Benefits Management Services, Medical Advisory Panel, VISN Pharmacist Executives and Office of Public Health

The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. **THE CLINICIAN SHOULD UTILIZE THIS GUIDANCE AND INTERPRET IT IN THE CLINICAL CONTEXT OF THE INDIVIDUAL PATIENT. INDIVIDUAL CASES THAT ARE EXCEPTIONS TO THE EXCLUSION AND INCLUSION CRITERIA SHOULD BE ADJUDICATED AT THE LOCAL FACILITY ACCORDING TO THE POLICY AND PROCEDURES OF ITS P&T COMMITTEE AND PHARMACY SERVICES.** *The Product Information should be consulted for detailed prescribing information. See the VA National PBM-MAP-VPE Monograph on this drug at www.pbm.va.gov or http://vaww.pbm.va.gov for further information.*

Exclusion Criteria *If the answer to ANY item below is met, then the patient should NOT receive sofosbuvir-based regimen without local adjudication.*

☐ Limited Life Expectancy (refer to issues for consideration)

☐ Patients with severe renal impairment (eGFR<30mL/min/1.73m^2), end-stage renal disease or on hemodialysis (Refer to elbasvir/grazoprevir CFU for this population).

☐ Patients who have virologically failed prior treatment with a NS5A inhibitor based regimen (e.g., ledipasvir, ombitasvir, daclatasvir or elbasvir) (applies to LDV/SOF but not to SOF alone) unless resistance testing indicates susceptibility to ledipasvir

☐ Documented ongoing nonadherence to prescribed medications or medical treatment, failure to complete hepatitis C virus (HCV) disease evaluation appointments and procedures or unable to commit to scheduled follow-up/monitoring for the duration of treatment

☐ Known hypersensitivity to any component of the planned treatment regimen

☐ HCV **genotype 2** infection (applies only to LDV/SOF)

Drug interactions

☐ For sofosbuvir, coadministration with rifampin, rifabutin, rifapentine, St. John's wort, anticonvulsants (i.e., carbamazepine, phenytoin, phenobarbital, oxcarbazepine), or tipranavir/ritonavir.

☐ For sofosbuvir in combination with another direct acting antiviral, co-administration of amiodarone (refer to Issues for Consideration)

☐ For ledipasvir/sofosbuvir, coadministration with rifampin, rifabutin, rifapentine, St. John's wort, carbamazepine, phenytoin, phenobarbital, oxcarbazepine, elvitegravir/cobicistat/emtricitabine/tenofovir, tipranavir/ritonavir, simeprevir, rosuvastatin, or amiodarone

When a sofosbuvir-containing regimen is used in combination with peginterferon and/or ribavirin

☐ Any contraindications and/or intolerance to peginterferon or ribavirin if sofosbuvir-containing regimen to be used in combination with peginterferon and/or ribavirin

- Contraindication and/or intolerance to ribavirin: Contraindication is defined as history of significant or unstable cardiac disease, known pregnancy, positive pregnancy test, and men whose female partner is pregnant or plan to become pregnant, known hypersensitivity reaction, and/or significant anemia (i.e. symptomatic or baseline hemoglobin <10g/dL) and/or history of *significant* adverse events with previous ribavirin-containing regimen. **Please note that history of anemia related to ribavirin-containing regimen should be evaluated in context of PBM CFU for ESA (i.e., ribavirin dose reduction to 600mg must have been instituted prior to consideration of ESA use) and does not necessarily constitute intolerance.

Inclusion Criteria *The answers to ALL OF THE FOLLOWING must be fulfilled in order to meet criteria.*

☐ Under care of and/or in collaboration with an experienced VA HCV practitioner

☐ Adherence counseling performed including laboratory follow-up and documented understanding by patient

☐ HCV Genotype 1, 4 5 or 6

☐ For HCV Genotype 3, ledipasvir/sofosbuvir (Harvoni) should only include patients without cirrhosis (refer to daclatasvir plus sofosbuvir CFU for options in cirrhotics)

☐ Treatment regimen and duration based upon HCV Genotype and patient characteristics according to the dosage and administration section below

For women of childbearing potential receiving ribavirin or who have a male partner receiving ribavirin:

☐ When ledipasvir/sofosbuvir or sofosbuvir is used in combination with ribavirin therapy (which is pregnancy category X), the ribavirin should not be started unless a report of a negative pregnancy test has been obtained immediately prior to initiation of therapy. Two effective methods of contraception should be used during treatment with sofosbuvir and concomitant ribavirin, and for 6 months after treatment has concluded. Routine monthly pregnancy tests must be performed during this time.

Dosage, Administration

Treatment regimen and duration are based upon patient characteristics as described in the Table below**.**

Ledipasvir/sofosbuvir regimen (i.e., two-drug fixed-dose combination product)

One tablet (90mg of ledipasvir and 400mg of sofosbuvir) taken orally once daily with or without food

Sofosbuvir and ribavirin regimen

Sofosbuvir 400mg orally once daily with or without food in combination with ribavirin (in 2 divided doses) with food (<75 kg: 1000 mg/day or ≥75 kg: 1200 mg/day).

Sofosbuvir, peginterferon, and ribavirin regimen

Sofosbuvir 400mg orally once daily with or without food *plus* peginterferon (either peginterferon alfa-2a 180 mcg/week or alfa-2b 1.5 mcg/kg/week) in combination with ribavirin (in 2 divided doses) with food (<75 kg: 1000 mg/day or ≥75 kg: 1200 mg/day)

Population includes patients with HCV monoinfected, HCV/HIV-1 co-infected, or hepatocellular carcinoma (HCC)[a]	**Dosage Regimens**	**Total treatment duration**
HCV Genotype 1		
Treatment-naïve without cirrhosis[b]		
HCV RNA <6 million IU/mL	Ledipasvir/sofosbuvir	8 weeks
HCV RNA ≥6 million IU/mL	Ledipasvir/sofosbuvir	12 weeks
Treatment-naïve with cirrhosis	Ledipasvir/sofosbuvir	12 weeks
Treatment-experienced[c] without cirrhosis	Ledipasvir/sofosbuvir	12 weeks
Treatment-experienced[c] with cirrhosis[d]	Ledipasvir/sofosbuvir OR Ledipasvir/sofosbuvir and ribavirin	24 weeks 12 weeks
Decompensated cirrhosis[d]	Ledipasvir/sofosbuvir and ribavirin (initiate ribavirin at 600mg/day and titrate up as tolerated) OR Ledipasvir/sofosbuvir (if unable to tolerate ribavirin)	12 weeks 24 weeks
HCV Genotype 2[d]		
Treatment-naïve without cirrhosis	Sofosbuvir plus ribavirin	12 weeks
Treatment-naïve with cirrhosis	Sofosbuvir plus ribavirin	16 weeks
Treatment-experienced without cirrhosis	Sofosbuvir plus ribavirin	12 or 16 weeks
Treatment-experienced with cirrhosis	Sofosbuvir plus ribavirin	16 weeks
HCV Genotype 3[d]		
Treatment-naïve without cirrhosis	Ledipasvir/sofosbuvir plus ribavirin	12 weeks
Treatment-naïve with compensated cirrhosis	Refer to the daclatasvir plus sofosbuvir CFU OR Sofosbuvir plus peginterferon and ribavirin	------- 12 weeks
Treatment-experienced (PEG/riba only) without cirrhosis	Ledipasvir/sofosbuvir plus ribavirin OR Sofosbuvir plus peginterferon and ribavirin	12 weeks OR 12 weeks
Treatment-experienced (PEG/riba only) with compensated cirrhosis	Refer to the daclatasvir plus sofosbuvir CFU OR Sofosbuvir plus peginterferon and ribavirin	------- 12 week

Decompensated cirrhosis	Refer to daclatasvir plus sofosbuvir CFU	-----
HCV Genotype 4, 5, or 6	Ledipasvir/sofosbuvir	12 weeks

[a]Refer to Issues for Consideration for alternative treatment options including patients with decompensated cirrhosis, and pre- and post-transplant.
[b]HCV/HIV co-infected patients who are treatment-naïve without cirrhosis should receive 12 weeks of ledipasvir/sofosbuvir independent of baseline HCV RNA
[c]In clinical trials, treatment-experienced was defined as previous peginterferon/ribavirin with or without an NS3/4A protease inhibitor
[d]Refer to Issues for Consideration for additional information

Recommended Monitoring

In addition to standard clinical and laboratory monitoring in a patient receiving HCV therapy, the following monitoring is recommended for sofosbuvir-based regimen:

- **Hematologic adverse events (anemia) if co-administered with ribavirin:** Complete blood count should be obtained at baseline and at treatment weeks 2, 4, 8, and 12, and at other time points, as clinically appropriate. Initial management of anemia should consist of ribavirin dose reduction for hemoglobin <10g/dL or sooner if clinically indicated; for additional monitoring and management of Hepatitis C treatment-related anemia refer to the PBM CFU for Recombinant Erythropoietin.
- Virologic monitoring **should be assessed to determine response to treatment. Patients receiving any sofosbuvir-based regimen should have HCV RNA assessed at week 4 of treatment; if the HCV RNA is detectable at week 4 or at any time point thereafter, HCV RNA should be reassessed in 2 weeks. If the repeated HCV RNA level has increased (i.e., >1 $\log_{10}$ IU/mL from nadir), discontinuation of all therapy should be strongly considered.**
- **Sustained Viral Response (SVR) or non-response** should be determined by measurement of HCV RNA 12 weeks after stopping treatment.
- **Ongoing assessment of treatment adherence** including medical appointments, laboratory follow-up and medications should be performed.
- **Monthly pregnancy tests** for women of childbearing potential receiving ribavirin

Issues for Consideration

Treatment Considerations:

- **In genotype 1 patients who are treatment-naïve without cirrhosis,** the difference in SVR between subjects receiving 8 weeks of ledipasvir/sofosbuvir and 12 weeks of ledipasvir/sofosbuvir was –2.3% (97.5% CI –7.2% to 2.5%). Among subjects with a baseline HCV RNA <6 million IU/mL, the SVR was 97% (119/123) with 8 weeks of ledipasvir/sofosbuvir and 96% (126/131) with 12 weeks of ledipasvir/sofosbuvir.
- **In genotype 1 patients who had previous virological failure with an NS3-4A protease inhibitor,** ledipasvir/sofosbuvir has been shown to be effective. A 12 week regimen is FDA-approved for non-cirrhotic subjects who have failed prior HCV treatment (including regimens with a protease inhibitor) and 24 weeks of ledipasvir/sofosbuvir is FDA-approved regimen for cirrhotic subjects who have failed prior treatment. However, in a randomized, double-blind study comparing ledipasvir/sofosbuvir plus ribavirin for 12 weeks to ledipasvir/sofosbuvir for 24 weeks in cirrhotic patients who had previously failed NS3-4A protease-inhibitor based triple therapy with boceprevir or telaprevir; SVR was achieved in 96% (74/77) of patients treated with ledipasvir/sofosbuvir plus ribavirin for 12 weeks and in 75/77 (97%) of patients treated with ledipasvir/sofosbuvir for 24 weeks.
- **In genotype 1 patients who had previous virological failure with a sofosbuvir-based regimen,** in a Phase II trial of GT1-infected patients (29% of whom had cirrhosis) who initially failed SOF + PEG-IFN + RBV (n=25) or SOF + RBV (n=21), re-treatment with LDV/SOF + RBV for 12 weeks achieved SVR in 100% (25/25) with prior SOF + PEG-IFN + RBV experience and 95% (20/21) with prior SOF + RBV experience.
- **In genotype 2 patients**,
    - Among treatment-experienced patients from the VALENCE study, SVR was achieved in 91% (30/33) of patients without cirrhosis and 88% (7/8) in those with cirrhosis treated with SOF + RBV for 12 weeks. In the FUSION study, a statistically insignificant increase in SVR rates was seen with extending SOF + RBV therapy from 12 to 16 weeks in prior nonresponders without cirrhosis (70% [7/10] vs. 88% [7/8], respectively) and in treatment-experienced patients with cirrhosis (60% [6/10] vs. 78% [7/9], respectively). Based on results from this small study, SOF + RBV for 16 weeks may be considered as an option in treatment-experienced patients; however, this 16-week regimen is not FDA approved. “Real-world” effectiveness data has also shown higher SVRs with longer treatment duration in treatment-experienced patients with cirrhosis.
    - For patients who have a contraindication or are intolerant to ribavirin, LDV/SOF for 12 weeks may be an alternative option. An open-label study of GT2 treatment-naïve and -experienced patients (n = 53) evaluated LDV/SOF for 8 or 12 weeks. The majority of patients were male (65-70%) and Caucasian (78-92%). In the 12-week arm, 26% were treatment-experienced and 8% had cirrhosis. SVR was achieved in 96% (25/26) with 12 weeks compared with 74% (20/27) with 8 weeks of LDV/SOF .
- **In genotype 3 patients**
    - In vitro, ledipasvir has minimal efficacy against HCV genotype 3. However, ledipasvir/sofosbuvir with or without ribavirin for 12 weeks was evaluated in an open-label study of 51 treatment naïve HCV genotype 3 patients. SVR rates were 100% (26/26) and 64% (16/25) in patients who received ledipasvir/sofosbuvir with and without ribavirin, respectively. In treatment experienced genotype 3 patients, ledipasvir/sofosbuvir plus ribavirin for 12 weeks resulted in SVR rates of 73% (16/22) and 89% (25/28) in those with and without cirrhosis, respectively. The high SVR rates observed in this study in non-cirrhotic patients (100% in treatment naive and 89% in treatment experienced) coupled with SVR rates of 89.5% from unpublished VA data in GT3 infected, non-cirrhotic patients that completed a full treatment course, provide the evidence to

support the use of LDV/SOF + RBV for 12 weeks in GT3 patients **without cirrhosis**. However, the use of LDF/SOV *without* ribavirin is **NOT** recommended for GT3 patients without cirrhosis due to lower SVR rates; thus, consideration may be given to daclatasvir in combination with sofosbuvir without ribavirin in patients whom ribavirin is not a treatment option and in whom treatment cannot be deferred. **The use of a LDV/SOF+RBV regimen in GT3 is not FDA approved**.
    - Because of lower SVRs observed in larger GT3 cirrhotic populations treated in real-world settings with LDV/SOF (59%, 36/61), LDV/SOF + RBV should **not** be used in GT3 patients with cirrhosis.
    - Baseline testing for NS5A RAVs is recommended for GT3 treatment-experienced including PEG/riba only and/or cirrhotic patients to determine treatment options. If the Y93H RAV is present, the patient should be informed of the potential for a lower chance of SVR. Consult a practitioner with expertise to weigh the risks versus benefits of treatment.
    - In a Phase ll open-label study of GT3 treatment-experienced patients treated with sofosbuvir, peginterferon, and ribavirin for 12 weeks, SVR occurred in 83% (10/12) of patients without cirrhosis and 83% (10/12) of those with cirrhosis. **This regimen is not FDA approved.**
- **Populations Unlikely to Benefit from HCV Treatment:** According to AASLD/IDSA HCV Guidelines, "patients with limited life expectancy for whom HCV therapy would not improve symptoms or prognosis do not require treatment. Chronic hepatitis C is associated with a wide range of comorbid conditions. Little evidence exists to support initiation of HCV treatment in patients with limited life expectancy (less than 12 months) due to non–liver-related comorbid conditions. For these patients, the benefits of HCV treatment are unlikely to be realized, and palliative care strategies should take precedence.".

Use in Specific Populations (refer to Prescribing Information for comprehensive list of use in specific populations):

- **HIV:** Co-infected patients should be managed in consultation with an experienced HIV provider.
- **Decompensated cirrhosis:**
    - In Genotype 1 and 4 patients, ledipasvir/sofosbuvir plus ribavirin (ribavirin initiated at 600mg and titrated upwards as tolerated) for 12 and 24 weeks has been evaluated in patients with Child Pugh B and C decompensated cirrhosis. SVR rates for those with Child Pugh B treated for 12 and 24 weeks were 87% (26/30) and 89% (24/27) respectively. SVR rates for those with Child Pugh C treated for 12 and 24 weeks were 86% (19/22) and 90% (18/20) respectively. Due to safety concerns, patients with decompensated liver disease should not receive a regimen containing peginterferon and/or a NS3-4A protease inhibitor. **Treatment of patients with decompensated cirrhosis should be managed by physicians with extensive experience in the treatment of patients with advanced liver disease**
    - In Genotype 2, 3, 5 and 6 patients, limited/no data exists and **care should be managed by physicians with extensive experience in the treatment of patients with advanced liver disease**. LDV/SOF should not be used in patients with GT 2 or in GT 3 patients with decompensated cirrhosis as it has not been shown to be efficacious.
- **Hepatocellular Carcinoma (HCC) or other cancer:** It is reasonable to treat HCV in any patient with HCC, history HCC, or other malignancy *if there is a high likelihood that the cancer has been cured*. Curative treatments for solitary or early stage HCCs within Milan criteria include resection and thermal ablation as well as liver transplantation (TACE, radioembolization, radiation therapy and targeted/chemotherapy are NOT considered curative). For those receiving resection or thermal ablation, if staging studies indicate good likelihood of success (absence of macrovascular invasion, clear margins, etc.) and if follow-up restaging studies show no evidence of cancer recurrence, then treatment of HCV may be offered.
- **Hepatic Impairment:**
    - Ledipasvir/sofosbuvir: No dosage adjustment is necessary for patients with mild, moderate or severe hepatic impairment.
    - Sofosbuvir: No dosage adjustment is necessary for patients with mild, moderate or severe hepatic impairment.
- **Pre-liver transplant (also see decompensated cirrhosis and HCC bullet above): <u>The decision to treat *any* patient awaiting transplantation should be made in consultation with the transplant center where the patient is listed and determined on a case by case basis</u>**. Close collaboration with the patient's transplant center is necessary to determine the timing of treatment initiation (pre- or post-) or whether treatment is appropriate given patient's prognosis.
- **Post-liver transplant:**
    - In Genotypes 1 and 4, ledipasvir/sofosbuvir plus ribavirin for 12 and 24 weeks was evaluated in post-liver transplant patients with stage F0-F3 disease, Child-Pugh A, B or C disease. SVR in patients without cirrhosis (METAVIR F0 – F3) was 96-98% with ledipasvir/sofosbuvir plus ribavirin for 12 weeks or 24 weeks. Among patients with cirrhosis, the SVR rates with Child-Pugh A was 96%, 83-85% for Child-Pugh B, and 60- 67% for Child-Pugh C with ledipasvir/sofosbuvir plus ribavirin for 12 weeks or 24 weeks, respectively.
    - In Genotypes 1, 3, and 4, sofosbuvir plus ribavirin for 24 weeks has been evaluated in two small Phase II trials of post-transplant patients with HCV. In one trial, SVR was achieved in 77% (31/40) of post-transplant patients. In the other trial (a compassionate use program), SVR was achieved in 60% (19/32) in patients receiving sofosbuvir and ribavirin and 50% (6/12) in patients receiving sofosbuvir, ribavirin and peginterferon. Because of the severity of the HCV disease in the patients at the time of treatment initiation, 15 patients died of progressive liver disease during the treatment period.
    - In Genotype 2, 5 and 6, no data exist though responses with sofosbuvir plus ribavirin are expected to be similar to those observed with other genotypes. The decision to treat these patients should be discussed and managed in coordination with the transplant center.
    - **Any sofosbuvir-based regimen should only be used in patients who are being actively managed by physicians with extensive experience in the treatment of post-transplant patients**. Close collaboration with the patient's transplant center is necessary to determine the timing of treatment initiation.
- **Renal Impairment:**
    - Ledipasvir/sofosbuvir: No dosage adjustment is necessary for patients receiving ledipasvir/sofosbuvir with mild or moderate renal impairment; the fixed-dose combination was not studied in patients with severe renal impairment (eGFR<30mL/min/1.73m^2), end-stage renal disease or on hemodialysis.

  - Sofosbuvir: No dosage adjustment is necessary for patients receiving sofosbuvir with mild or moderate renal impairment; sofosbuvir was not studied in patients with severe renal impairment (eGFR<30mL/min/1.73m^2), end-stage renal disease or on hemodialysis. The major metabolite of sofosbuvir is renally excreted and will accumulate in subjects with eGFR <30 mL/min/1.73m^2.
- **Substance or Alcohol Use**: All patients should be evaluated for current alcohol and other substance use, with validated screening instruments. Patients with active substance or alcohol use disorders may be considered for therapy on a case-by-case basis, and care should be coordinated with substance use treatment specialists as needed. **Thus, automatic disqualification of patients as treatment candidates based on a specific length of abstinence is unwarranted and is strongly discouraged**.
- **Mental Health Conditions:** HCV-infected patients with severe mental health conditions (e.g., psychotic disorders, bipolar disorder, major depression, posttraumatic stress disorder), as documented by psychiatric evaluation, who are engaged in mental health treatment should be considered for therapy on a case-by-case basis. The use of interferon-containing regimens is associated with worsening of these conditions. Patients should be managed in collaboration with Mental Health providers to determine the risks versus benefits of treatment and potential treatment options.
- **Hepatitis B:** No safety and efficacy data are available in this population; prescribing information states that no dosage adjustments are needed for sofosbuvir or ledipasvir/sofosbuvir for patients receiving tenofovir, entecavir or lamivudine.

Drug-interactions:

- Consult the prescribing information prior to use of sofosbuvir-based regimen for potential drug interactions
  - Both ledipasvir and sofosbuvir are substrates of drug transporter P-gp and breast cancer resistance protein (BCRP); drugs that are potent P-gp inducers in the intestine (e.g., rifampin, St. John's wort) may significantly decrease sofosbuvir and ledipasvir plasma concentrations.
  - Ledipasvir is an inhibitor of the drug transporter P-gp and BCRP and may increase intestinal absorption of coadministered substrates for these transporters.
- Drugs that increase gastric pH are expected to decrease absorption and blood concentration of ledipasvir.
  - Separate antacids and ledipasvir/sofosbuvir administration by 4 hours.
  - H2-receptor antagonists may be administered simultaneously with or 12 hours apart from ledipasvir/sofosbuvir at a dose that does not exceed doses comparable to famotidine 40mg twice daily
  - Proton-pump inhibitor doses comparable to omeprazole 20mg or lower can be administered simultaneously with ledipasvir/sofosbuvir under fasted conditions
- **Bradycardia with amiodarone coadministration:** Serious symptomatic bradycardia may occur in patients taking amiodarone, particularly in patients also receiving beta blockers, or those with underlying cardiac comorbidities and/or advanced liver disease. Coadministration of amiodarone with LDV/SOF or SOF with another direct acting antiviral is not recommended. In patients without alternative, viable treatment options, cardiac monitoring is recommended.

Education and Screening:

- Counsel patient on general liver health, especially abstaining from alcohol use and limiting acetaminophen use to 2g/day.
- Assess if patient previously screened and/or vaccinated for Hepatitis A and Hepatitis B vaccines; consideration vaccination if appropriate.
- Assess if patient previously screened for HIV; if not, consider testing for HIV.

Additional Resources:

- Refer to VA Office of Public Health Intranet Site http://vaww.hepatitis.va.gov

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